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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,789	MIYATA, TOSHIO	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,12 and 15-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,12 and 15-38* is/are rejected.

7)☒ Claim(s) *15, 17, 18, 29, 33-34, and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *November 7, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 7, 9, 12, and 15-38 are pending. The Examiner acknowledges receipt on November 7, 2005 of an Information Disclosure Statement (PTO-1449), a terminal disclaimer regarding copending application 11/093,950, and Applicant's Remarks regarding the previous office action, mailed August 8, 2005.

Specification

The disclosure is objected to because of the following informalities: "butyl" is misspelled on page 6, line 21 of the specification as "buthyl".

Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims 15, 17, 18, 29, 33-34, and 36 are objected to because of the following informalities: claim 15 has unnecessary commas in line 1, after the word "method"; in line 2, after the word "immobilized:" and the word "fluid" in line 3 should be "fluids." The word "parameter" in line 2 of claim 17 should be plural ("parameters"). The comma in claim 18, line 3, after the word "bonding" is unnecessary. The comma after the word "shape" in claim 29, line 3 is unnecessary. The definite article "the" in claims 33, line 1 and claim 36, line 2 should be removed to agree with the subject's plural form. The word "agent" in claim 34, line 2 should be plural (i.e. "agents"). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 7, 16-19, 22, 29, and 32-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 15, 17, 29, 32, and 34 consist of one or more improper Markush groups. A proper Markush group must be written in the alternative. See MPEP § 2173.05(h).

Claim 15 recites the limitation "the blood purification" in line 4. There is insufficient antecedent basis for this limitation in the claim.

The remaining claims are rejected as being dependent upon a rejected claim.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7, 9, 23, 29, 30 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Keogh (U.S. Patent No. 5,928,916).

It is noted that claim 34 is written as a "method for," which may be interpreted as a "use claim" or a "method claim." If interpreted as a "use claim" the "method for" would be given little to no weight. The Examiner has interpreted this claim as a method claim and suggests that Applicant amend claim 34 to read "method of."

Keogh discloses a method involving combining at least one biomolecule comprising a negatively charged moiety with a material comprising at least one positively charged **biguanide moiety** ($RNHC(NH)NHC(NH)NH_2$) to form an immobilized biomolecule on a medical device biomaterial surface through an ionic bond (column 3, lines 15-22; claims 1a and 2).

Keogh discloses that a "biomaterial" is a material that is substantially insoluble in body fluids, which is designed and constructed to be placed in or onto the body or **to contact fluid of the body** (column 3, lines 59-62),

Keogh discloses that the guanidinium group's features make it a very attractive moiety for incorporation onto biomaterial surfaces. For example, its high basicity (a pK_a of 13.5 for guanidinium itself) allows it to remain protonated over a much wider range of pH than does the ammonium group. In fact, at physiological pH, all but a small fraction of the guanidine molecules will exist as positively charged species (column 4, lines 51-57). Metformin contains two guanidine-derived groups.

Keogh discloses that biomaterials comprising amines on their surface may be modified to comprise guanidino moieties by reaction with O-methylisourea or S-methylisothiourea to yield substituted guanidines (column 5, lines 6-8). This modification would be a means to covalently attach a biguanide to a biomaterial surface comprising amines.

Keogh discloses that his invented biomaterials, which do not have amines on their surface, may be aminated readily through a number of methods well known in the art (column 5, lines 41-43). The implementation of this disclosure increases the number of biomaterials that could be used as carriers upon which biguanides could be immobilized.

Keogh discloses that there are a number of methods well known in the art to functionalize various moieties to monoguanidines or **biguanides (diguanides)** (column 5, lines 63-67 and column 6, lines 1-9).

Keogh discloses that molecules containing at least one guanidino moiety and at least one reactive moiety may be **grafted** to a biomaterial surface through the reactive moiety (column 6, lines 10-12). Metformin and other biguanides contain at least one guanidino moiety.

Keogh discloses that compounds such as 1-dodecylguanidine, which comprise at least one guanidino moiety and a hydrophobic region, may be adsorbed from a solution onto the surface of a hydrophobic biomaterial (column 6, lines 38-41). Biguanides contain at least one guanidino moiety and can be appropriately derivatized to contain a hydrophobic region. Adsorption reads on the term "physical adsorption."

Keogh discloses that biomaterials may be furnished with a net negative charge on their surface, such as polyethylene following exposure to sulfuric acid comprising potassium permanganate, and may be exposed subsequently to guanidino comprising compounds, thereby reversing the surface polarity of the biomaterial surface from negative to positive (column 6, lines 52-57).

Keogh discloses that his method can be used to modify several different substrates, including, **aluminum oxide** (i.e. **alumina**), **polymers** (e.g. **polyamides, polycarbonates, polyethers, polyesters, polyolefins, rubber**), minerals or ceramics, organic materials, (e.g. **cellulose**), and other materials (e.g. **glass**) (column 8, lines 11-28). Alumina, and glass are examples of inorganic materials. Polyamides, polycarbonates, etc. are examples of synthetic

organic macromolecules. The term "macromolecule" is synonymous with the word "polymer." Cellulose is an example of a naturally occurring polysaccharide.

Keogh discloses that one method of his invention may be used to modify substrates of **any shape or form including tubular, sheet, rod**, and articles of proper shape or for use in a number of medical devices, including **dialysis membranes, ultrafiltration membranes, blood handling equipment, vascular stents, blood bags**, etc. (col. 8, lines 29-42).

Claims 37-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Gatlin et al. (U.S. Patent No. 6,559,188).

Gatlin discloses that his invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide (I) or repaglinide and at least one other antidiabetic compound, including **metformin** for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases (e.g. type 2 diabetes) (abstract).

Gatlin discloses that each **oral formulation (composition)** according to the present invention may additionally comprise inert constituents including pharmaceutically acceptable carriers, diluents, fillers, solubilizing or emulsifying agents and salts as is well-known in the art (col. 15, lines 26-30).

Gatlin discloses that the anti-diabetic drugs or combinations thereof can be combined as the active ingredients in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., **oral or parenteral (including intravenous)** (col. 16, lines 63-67 and col. 17, lines 1-2).

Gatlin discloses for these purposes, the combinations of the present invention may be administered **orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques)**, by **inhalation** spray (col. 17, lines 51-55).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 7, 9, 12, 15-17, 19-24, and 31-37 under 35 U.S.C. 103(a) as being unpatentable over Miyata, T. et al. (*Kidney International*, **1999**, *55*, pp 389-399) in view of Ruggiero-López, D. et al. (*Biochem. Pharmacol.* **1999**, *58*, pp 1765-1773) **is withdrawn**, in light of the instant application's priority date of October 6, 1999.

The rejection of claims 18 and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Miyata, T. et al. (*Kidney International*, **1999**, *55*, pp 389-399) and Ruggiero-López, D. et al. (*Biochem. Pharmacol.* **1999**, *58*, pp 1765-1773) and in view of Keogh (U.S. patent 5,928,916) **is withdrawn**, in light of the instant application's priority date of October 6, 1999.

The rejection of claims 34-36 and 38 under 35 U.S.C. 103(a) as being unpatentable over Ikeda, H. et al. (U.S. patent 5,952,356) in view of Ruggiero-López, D. et al. (*Biochem. Pharmacol.* **1999**, *58*, pp 1765-1773) **is withdrawn**, in light of the instant application's priority date of October 6, 1999.

New rejections under 35 U.S.C. 103(a) follow below.

Claims 7, 9, 12, 15-17, 19-24, and 31-37 under 35 U.S.C. 103(a) as being unpatentable over Miyata, T. et al. (*Kidney International*, 1999, *55*, pp 389-399) in view of

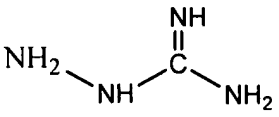
Ruggiero-López, D. et al. (*Diabetologia.* 1997, 40: A310 from PTO-1449 submitted on November 3, 2004).

It is noted that claims 15, 32, and 34 are written as "method for," which may be interpreted as a "use claim" or a "method claim." If interpreted as a "use claim" the "method for" would be given little to no weight. The Examiner has interpreted these claims as method claims and suggests that Applicant amend claims 15, 32, and 34 to read "method of."

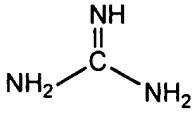
Miyata et al. teach that Advance Glycation End products (AGEs) are linked to plasma proteins (mainly albumin) and are not effectively removed by hemodialysis and peritoneal dialysis. AGE accumulation in plasma proteins cannot by attributed to decreased renal clearance of protein-linked carboxymethyllysine (CML) and pentosidine (last sentence of the 3rd paragraph in the right hand column on page 390). AGEs have been implicated in the pathogenesis of several diseases, including diabetes and uremia (1st sentence in the body of the text on page 389, left hand column). The formation of AGEs is associated with the increased concentration in blood plasma of small reactive carbonyl compounds (4th sentence in left hand column on page 389).

Miyata, T. et al. suggest the development of less toxic more specific carbonyl stress inhibitors **immobilized in cartridges** may enhance extraction of reactive carbonyl compounds **from blood during dialysis** for the treatment of conditions in which reactive carbonyl compounds and carbonyl stress end products are implicated (e.g. diabetes) (Last 3 sentences in the "Carbonyl stress quenching" subsection, p 396). The term cartridge is interpreted to read on a carrier having one of the shapes listed in claim 7. The phrase "enhance extraction of reactive carbonyl compounds from blood during dialysis" implies the use of a hemodialysis membrane.

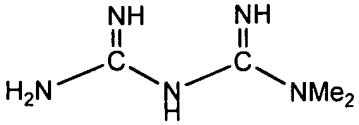
Aminoguanidine



Guanidine



Metformin (a biguanide)



Miyata, T. teaches that carbonyl stress end products are formed by carbonyl amine chemistry between carbonyl compounds and protein amino groups (1st sentence of the section entitled, "Carbonyl stress quenching" on page 396). Ketones and aldehydes are examples of carbonyl compounds that have a well known reaction chemistry with primary amino groups to yield imines, also called Schiff bases, whereas their reaction with hydrazine and its derivatives results in compounds called hydrazones (Solomon, T. W. G *Organic Chemistry, 5th edn.* John Wiley & Sons, Inc.: New York, 1992, pp 701-704).

Miyata, T. teaches that **aminoguanidine** and thiazolidine derivatives have been used to inhibit carbonyl stress by a similar mechanism, read as the reaction of their hydrazine nitrogens with reactive carbonyl species to form hydrazones (sentences 2-5 in the section entitled, "Carbonyl stress quenching" on page 396).

Miyata lacks the specific teaching or suggestion of using a biguanide compound to inhibit carbonyl stress.

Aminoguanidine and metformin (dimethylbiguanide) are guanidine derivatives. See structures below.

Ruggiero-López teaches that the reaction between reducing sugars and amino structures in proteins has been shown to play a role in the development of the characteristic tissue pathology of diabetes. Guanidine compounds inhibit this process by blocking the reaction of amino groups with glucose or the dicarbonyl compounds derived from them. Glycoxidation of

albumin by dicarbonyl compounds, such as glyoxal and methylglyoxal, was reduced by 30% and 50%, respectively, in the presence of 1 mM **metformin**. Ruggiero-López concludes that their results suggest **metformin** could also decrease AGE formation by reaction with reducing sugars or glycoxidation intermediates (1st two sentences and last sentence).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Miyata and Ruggiero-Lopez to alleviate the carbonyl stress state in a person's blood via hemodialysis or contacting their blood or peritoneal dialysate with a carrier comprised of immobilized AGE-inhibitors, such as the biguanide, metformin. The motivation to combine these teachings comes from Miyata who teaches the need to inhibit the formation of AGEs and promote their removal from blood and peritoneal dialysate. Miyata states that hemodialysis and peritoneal dialysis are unable to remove AGEs and suggests that this problem could be addressed by immobilizing carbonyl stress inhibitors in cartridges used during dialysis therapy. Motivation for a person of ordinary skill in the art to use biguanide agents immobilized in a carrier to remove AGEs *in vivo* is provided by Ruggiero-Lopez who teaches that metformin was able to inhibit the formation of albumin-AGEs. A skilled artisan would also be motivated to use biguanides to remove AGEs due to the structural similarity of aminoguanidine, used to inhibit carbonyl stress (Miyata), and the well known reactivity of ketones and aldehydes with compounds having amino and/or hydrazine moieties.

A skilled artisan at the time of the instant invention would have had a reasonable expectation of success in using carriers containing immobilized biguanide agents to remove AGEs, because Ruggiero-Lopez' results suggest metformin consumes reactive carbonyl

compounds that lead to the formation of AGEs and aminoguanidine is a well known carbonyl stress inhibitor (Miyata).

Miyata and Ruggiero-Lopez do not teach a specific carrier shape or motivation to modify a carrier's shape, however, the choice of carrier shape and any subsequent modification of a carrier's shape and physical dimensions, such as length, diameter, and thickness are obvious routine modifications that a capable skilled artisan would undertake to optimize the performance of materials used in various processes. For example, if one had a square-shaped carrier and needed a spherical-shaped carrier for use in a different dialysis machine, one would appropriately adjust the carrier shape and dimensions to conform to the physical constraints of the carrier location within the different dialysis machine (e.g. shape, size, length, thickness, etc.). Increasing or decreasing the size of a given material used would also change its surface area. Therefore, changing surface area is also an obvious routine modification in the art.

Claims 18 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyata, T. et al. (*Kidney International*, 1999, *55*, pp 389-399) in view of Ruggiero-López, D. et al. (*Diabetologia.* 1997, 40: A310 from PTO-1449 submitted on November 3, 2004) as applied to claims 7, 9, 12, 15-17, 19-24, and 31-37 above, and further in view of Keogh (U.S. patent 5,928,916).

The teachings of Miyata, T. in view of Ruggiero-Lopez have been set forth above.

The combined teachings of Miyata and Ruggiero-López lack a means of immobilizing biguanide agents onto carriers of various shapes and materials.

The disclosures/teachings of Keogh (USPN 5,928,916) have been set forth above in the 102(e) rejection above.

A person of ordinary skill in the art at the time of the instant invention would have been motivated to combine the teachings of Miyata, Ruggiero-Lopez, and Keogh because all these inventors teach the use of guanidine-containing compounds in medical applications. Miyata provides the motivation for the immobilization of carbonyl stress inhibitors in carriers (e.g. cartridges (supra)) used in dialysis therapy (i.e. blood, blood plasma, peritoneal dialysate would contact carbonyl stress inhibitors) and Ruggiero-Lopez provides the motivation for using biguanides as carbonyl stress inhibitors. Keogh's teachings would have provided a skilled artisan with the necessary know-how needed to immobilize biguanides onto biomaterials. For these aforementioned reasons, the teachings of the combined prior art references would have provided a person of ordinary skill in the art a reasonable expectation of success. The immobilized biguanide agents are expected to remain positively charged and thus immobilized on the carriers used when exposed to body fluids at physiological pH conditions.

Claims 34-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikeda, H. et al. (U.S. patent 5,952,356) in view of Ruggiero-López, D. et al. (*Diabetologia.* 1997, 40: A310; from PTO-1449 submitted on November 3, 2004).

Applicant's claims do not require immobilization of the biguanide, nor do is a carrier for administration of the biguanide agent specified. The intended use of the biguanide agent for the removal of carbonyl compounds is not given any weight in the evaluation of the claim, as this is considered a property of these compounds.

Ikeda, H. et al. teach a pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one other active, including a **biguanide** (column 2, lines 1-8).

Ikeda teaches that **biguanides** are drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress hepatic gluconeogenesis, and inhibit fatty acid oxidation (column 11, lines 46-50).

Ikeda teaches that some examples of biguanides are **phenformin, metformin, and buformin** (column 11, lines 50-51).

Ikeda teaches that the dosage form for said pharmaceutical composition includes such oral dosage forms and non-oral dosage forms, including **injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections)**. These dosage forms can be manufactured by the techniques conventionally used in pharmaceutical procedures (column 13, lines 51-58).

Ikeda teaches that his pharmaceutical compositions have a low toxicity and can be used safely in mammals (e.g. humans, etc.) (column 14, lines 58-60).

Ikeda lacks the express teaching that biguanide agents also function as carbonyl stress inhibitors.

The teachings of Ruggiero-López have been set forth above.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Ikeda and Ruggiero-Lopez to administer a biguanide agent via an injection to capitalize on the known carbonyl stress inhibition properties of metformin and other biguanides (Ruggiero-López). It is understood that a non-oral dosage form (e.g. intravenous injections) would contact one or more biguanides with a body fluid, such as blood, blood plasma, and peritoneal dialysate. A skilled artisan at the time of the instant

invention would therefore have had a reasonable expectation of successfully contacting one or more body fluids via injection of one or more biguanide agents and inhibiting carbonyl stress.

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the art.

Double Patenting

The provisional rejection of claims 32-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 14, 20-23, 28-31, 36-38, and 45 of copending Application No. 11,093,950 **is withdrawn**, in light of the terminal disclaimer submitted by the Applicant on November 7, 2005.

Claims 15, 23, 32, and 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,919,326 (USPN '326) in view of Ruggiero-López, D. et al. (*Diabetologia.* 1997, 40: A310; from PTO-1449 submitted on November 3, 2004).

Both sets of claims are drawn to methods of removing (i.e. trapping) carbonyl compounds from peritoneal dialysate. The difference between the claims of the instant application and those of USPN '326 is that those of USPN '326 do not specify the carbonyl-compound trapping agent. Ruggiero-López teaches that metformin was used to reduce the amount of AGEs formed from the reaction of albumin with active carbonyl compounds (glyoxal and methylglyoxal). It would have been obvious to a skilled artisan that metformin, a biguanide, could be used as a carbonyl-compound trapping agent. Therefore, claims 15, 23, 32, and 34 of the instant application are obvious over claims 1 and 2 of USPN '326 in view of Ruggiero-

López, D. et al. (*Diabetologia.* 1997, 40: A310; from PTO-1449 submitted on November 3, 2004).

Response to Arguments

Applicant's arguments with respect to claims 7, 9, 12, and 15-38 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

The specification is objected to because of minor informalities. Claims 7, 9, 12, and 15-38 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni (Paddy) Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Examiner

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER